REMARKS

Applicants have cancelled claim 70 without prejudice.

Applicants have amended claims 80 and 82 to specify that the hydroxypropyl methyl cellulose is a "low viscosity" hydroxypropyl methyl cellulose. Support for this amendment is found e.g. on page 6, line 2 and the examples.

Applicants have amended claim 80 to recite "...wherein the components are combined to allow the glyceryl behenate and the hydroxypropyl methylcellulose to form the matrix and the clarithromycin component is dispersed within the matrix; ..." Support for this amendment is found, e.g., on page 6, lines 12-13 "It has been found that by combining glyceryl behenate and HPMC there was obtained an exceptionally effective matrix for sustaining and controlling release of the active substance..."

Claims 70-72 and 76-84 stand rejected under 35 U.S.C. §112, first paragraph for purportedly lacking written description. Applicants disagree and in view of the following remarks and amendments to the claims request that the Examiner reconsider and withdraw the rejection.

The Office states that the Applicants have support for 42.01% and 43.47% clarithromycin but that the term "at least" and the term "about 42%" and "about 43%" are not supported by the specification. Although Applicants disagree, Applicants have amended the claims by deleting "at least." As amended, the claims comply with the written description requirement of §112, first paragraph. While the specification may not recite explicitly "about 42%" or "about 43%" the written description requirement does not require an explicit recitation of terms recited in the claims. The essential goal of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed. There is no *in haec verba* requirement; the newly added claim limitations must be supported in the specification but that

support may be through express, implicit, or inherent disclosure (see MPEP §1302.01). Applicants have provided such support.

Applicants have disclosed that the daily dose of 500 mg clarithromycin has to be imbedded in a relatively small matrix so that it is not hard to swallow (Background of the Invention page 1, lines 15-16). Applicants have demonstrated the production of tablets comprising 500mg clarithromycin; the tablets comprise about 42% and about 43% clarithromycin, i.e. 42.01% for example in Examples 2 and 3, and 43.47% in Examples 1, 4 and 5, respectively. Presented with Applicants' teachings, a person of skill in the pharmaceutical art would recognize that the inventor had possessions of pharmaceutical preparations containing "about 42%" and "about 43%." An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. See, e.g., *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000) (the written description "inquiry is a factual one and must be assessed on a case-by-case basis").

The foregoing demonstrates that Applicants have provided the necessary showing to support adequate written description of the current claims and request that the Examiner withdraw the rejection of the claims under 35 U.S.C. §112, first paragraph

Claims 72, 76-78, and 80-83 stand rejected under 35 U.S.C. §103(a) for purportedly being unpatentable over WO95/22319 ("Briskin") in view of U.S. Patent No. 5,811,120 ("Gibson") and for claim 82, METHOCEL and WO 98/42311 ("Akiyama") are relied upon for evidence. Applicants disagree. The combination of Briskin and Gibson, METHOCEL and Akiyama fail to teach or suggest the claimed compositions.

Applicants' claims recite a control release pharmaceutical formulation comprising particular components, i.e., clarithromycin, glyceryl behenate and low viscosity hydroxypropyl methyl cellulose (HPMC), in particular amounts, which provide for a controlled release of clarithromycin over a 24 hour period. The Office states that it would have been obvious to one of skill in the art at the time the invention was made to combine the teachings of Briskin and Gibson and utilize the instant hydrophilic binder (HPMC) (Office Action page 5, last paragraph). The Office states that one would have been motivated to substitute Briskin's hydrophilic binders (HPC and povidone), for HPMC with a reasonable expectation of similar results because, the Office contends, Gibson teaches HPMC, HPC and Povidone are conventional hydrophilic binders utilized in pharmaceutical compositions (Office Action paragraph spanning pages 5-6). However, even if one of skill in the pharmaceutical arts were to motivated to substitute the "conventional binders" of Briskin's formula 1b with HPMC then the modified formula 1b would comprise 36% HPMC, not 10.5% HPMC. At the time of this invention those of skill in the art appreciated that Carbopol is also a binder, see e.g., U.S. Patent No. 4,184,888, which states

> "To further facilitate tableting, a conventional tableting binder may optionally be employed . . . . Suitable binders include, . . . hydroxypropylmethyl cellulose . . . or a carboxypolymethylene polymer (carbomer)."
>
> Col. 3, lines 47 to 54.

Carbopol is a carbomer and thus a conventional binder and so Briskin teaches a formulation comprising the "binder" in a total weight percent of 36.5% (5.5% povidone, 5% HPC and 26% Carbopol), which is twice the maximum amount of HPMC recited in Applicants' claims.

In addition, those of skill in the art appreciate that different binders have different properties that confer different characteristics to pharmaceutical formulations and without a description of the properties of the three different binders in Briskin's formulation, Providone K90, a nondescript HPC and a

nondescript Carbopol, one of skill in the art would not be motivated to simply replace any of them with an HPMC with the expectation of similar effects. Evidence that those of skill in the art do not consider all PVPs, HPCs and HPMCs to be functionally equivalent, is found in U.S. Patent No. 5,126,145 ("Evenstad"), which states "hydroxypropylmethylcelluloses vary in their viscosity, methoxy content and hydroxypropoxyl content. Properties also vary." (Col. 3, lines 5-7). Evidence that those of skill in the pharmaceutical arts do not consider all HPCs and all HPMCs to be functionally equivalent is also found in Akiyama who distinguishes "low-substituted HPC" from other HPCs and HPMCs by describing it as "a material which swells a viscogenic agent" (see page 15, lines 16-24) and then describing viscogenic agents to include Carbopol™, HPC and HPMC. Evanstad also teaches the different functionality of high versus low viscosity HPMC: high viscosity provides sustained release whereas a water-soluble binder such a HPMC having binding properties has a much lower viscosity; typically a viscosity of less than 100cps such as Methocel E15. (Office Action page 11, first paragraph). Thus, not all HPCs and HPMCs are functionally equivalent. One of skill in the pharmaceutical arts could not reasonably predict the effect that substituting an HPMC for one or more of PVPK90, the uncharacterized HPC and the uncharacterized Carbopol would have on the characteristics of Briskin's formula 1b. Without any description of the HPC's and the Carbopol's properties, one in the pharmaceutical could not determine which other of a variety of compounds could be substituted for the Briskin binders and still have similar characteristics to formula 1b.

> A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning. See *Graham*, 383 U. S., at 36 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "'guard against slipping into the use of hindsight'" (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F. 2d 406, 412 (CA6 1964))).
>
> *KSR. v. Teleflex* 550 U. S. ____ (2007).

While the Office has proposed that one of skill in the art would substitute just two of the binders in Briskin's formula1b with a single HPMC to achieve an HPMC amount of 10.5%, such a substitution, considered within the context of the knowledge available to those of skill in the art at the time of the invention, would only be made in hindsight in light of Applicants' disclosure.

Thus, in view of the knowledge available to those of skill in the art at the time of this invention, Briskin in combination with Gibson fails to provide the necessary guidance and motivation for one of skill in the art to replace only two of Briskin's three "conventional binders" with any HPMC with the expectation of obtaining similar properties; and even if one were to replace Briskin's three "conventional binders" with an HPMC, even a low viscosity HPMC, the amount of HPMC would be twice the maximum amount recited in Applicants' claims. Thus Briskin in combination with Gibson considered within the state of the art, does not teach or suggest Applicants' invention.

Regarding claim 82, even if the formation of a viscous layer is a natural property of HPMC, the combination of Briskin and Gibson does not teach or suggest a formulation comprising a low viscosity HPMC and as such Briskin and Gibson also fail to teach or suggest claim 82.

In view of the foregoing remarks, Applicants request that the Examiner reconsider and withdraw the rejection of Claims 72, 76-78, 80-83 under 35 U.S.C. §103(a) for purportedly being unpatentable over Briskin in view of Gibson.

Claims 70-71 stand rejected under 35 U.S.C. §103(a) for purportedly being unpatentable over Briskin in view of Gibson as evidenced by METHOCEL™ and Akiyama for claim 82 and further in view of US Patent No. 5,126,145 ("Evenstad"). Applicants respectfully disagree.

The Office concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Briskin, Gibson and Evenstad and specifically utilize a low viscosity HPMC and that "a skilled artisan would have been motivated to use a low viscosity HPMC with a reasonable expectation of similar results since both Briskin and Gibson teach the use of the cellulose derivative for its binding property and Evenstad teaches the low viscosity cellulose derivative provide this function" (Office Action page 11). As discussed above, Evenstad and Akiyama demonstrate that all HPCs and HPMCs are not functionally equivalent and thus without a description of the HPCs and Carbopols in Briskin's formula 1b, the skilled artisan would not simply replace one or more of Briskin's "binders" with just another "binder" and expect to obtain similar results. And even if one of skill in the arts substituted the PVP, HPC and Carbopol with HPMC, such a substitution would not produce Applicants' claimed control-release formulations because the amount of HPMC needed for such a substitution, 36.5%, would be more than twice the maximum amount recited in Applicants' claims.

Furthermore, Evanstad is directed to improved controlled release formulations and Evenstad's solution for making the controlled release formulation is to use a high viscosity HPMC to achieve controlled or sustained release. Thus, Evenstad teaches away from using a low viscosity HPMC to produce a controlled release formulation, as required in Applicants' claims.

> . "When the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely non-obvious ...."
>
> *KSR Int'l Co. v Teleflex Inc.*
> 550 U.S. __ (2007).

The foregoing demonstrates that considered within the context of the state of the art at the time of filing, the combination of Briskin, Gibson, and Evenstad fails to teach or suggest the invention as claimed. Applicants request that the Examiner reconsider and withdraw the rejection of claims under 35 U.S.C. §103

over Briskin in view of Gibson as evidenced by METHOCEL™ and WO 98/42311 for claim 82 and further in view of US Patent No. 5,126,145 (Evenstad).

Claim 79 stands rejected under 35 U.S.C. §103(a) for purportedly being unpatentable over Briskin in view of Gibson as evidenced by METHOCEL™ and Akiyama for claim 82 further in view of US patent No. 5,656,295 ("Khan"). Applicants disagree.

The failure of Briskin, Gibson, METHOCEL™ and Akiyama to teach or suggest the claimed formulations have been discussed above. The deficiencies of these references are not compensated for by Khan. Khan simply teaches a delivery system coated with a coating layer. Khan fails to teach or suggest the particular formulation recited in Applicants' claim and without such a teaching or suggestion, its simple generic teaching that one may coat a delivery system combined with the disclosures of Briskin and Gibson, fails to render the claimed formulations obvious.

In view of the forgoing remarks, Applicants request that the Examiner reconsider and withdraw the rejection of claim 79 under 35 U.S.C. §103(a) in view of Briskin, Gibson, and Khan.

Claims 70-72, 76-84 stand rejected under 35 U.S.C. §103(a) for purportedly being unpatentatble over Akiyama in view of WO 98/14176 ("Farah"), US equivalent Patent No. 6,194,005. Applicants respectfully disagree.

Applicants claim a controlled-release formulation comprising glyceryl behenate, low viscosity hydroxypropyl methyl cellulose and clarithromycin in particular amounts, i.e., 10-36%, 13-18% and about 42% or about 43% respectively. In contrast, Akiyama teaches broad genera of compounds and of weight percentages including, e.g.:

> a swelling material that swells a viscogenic agent or accelerates the swell of a viscogenic agent caused by water (page 15, lines 16-19), in an amount of about 0.5 to 50 weight % (page 15, line 25-27)
>
> any type of viscogenic agent (page 17, lines 11-15), preferably having a viscosity of 3 to 50,000cps (page 17, lines 20-22), in amounts of about 0.005 to about 99% (page 19, lines 5-7),
>
> a polyglycerol fatty acid ester in an amount of 5-98% (page 12, lines 1-2),
>
> a antimicrobial substance in an amount of 0.0005-95% (page 26, lines 13-15),
>
> an optional coating material, and
>
> surfactants.

The Office states

> "Akiyama does not specify the glycerol fatty acid ester. Farah teaches a method for preparing a pharmaceutical composition with modified release of the active principle, comprising a matrix as lipid matrix agent, of an ester of behenic acid or alcohol. ...The lipid is used in an amount of 1-15% ...glycerol behenate is the preferred lipid for the matrix"
>
> (Office Action paragraph spanning pages 14-15)

and concludes that it would have been obvious to one of skill in the art at the time the invention was made to combine the teachings of Akiyama and Farah and utilize glyceryl behenate in Akiyama's composition. Yet Akiyama acknowledges that the selection of polyglycerol fatty acid ester is dependent on many factors, including the identity of the active compound and viscogenic agent:

> "the proper polyglycerol fatty acid ester can be selected with reference to the particular active ingredient (e.g., anti-HP agent, etc.), viscogenic agent, swelling material (e.g., curdlan, and/or low-substituted hydroxypropylcellulose, etc.), the particular combination thereof, and the objective form of the composition" (sentence spanning page 10-11).

Farah does not prepare any formulations with clarithromycin. Farah also demonstrates that their preparation method and the composition of the formulation could enhance or inhibit the release of active agent. Farah does not present any analysis of glyceryl behenate with clarithromycin. Therefore one of skill in the art based on Farah would have no reasonable expectation regarding how this active agent would interact with glyceral behenate.

Furthermore, Applicants' claims require a low viscosity HPMC at 13-18 weight percent. Akiyama's teaching that the viscogenic agent "may be selected from any agent that is capable of swelling in water." does not provide any sort of guidance as to the type of agent one should use. Akiyama's more specific teaching that "a suitable synthetic polymer has a viscosity 3-50,000cps and a basic or acidic polymer has a viscosity of about 100 to about 50,000cps" (see page 17, lines 20-22 and lines 24-28) is also insufficient to guide one of skill in the pharmaceutical arts to the claimed controlled release formulation comprising the particular amounts of low-viscosity HPMC, glyceral behenate and clarithromycin as recited in Applicants' claims. The Office previously cited Evenstad for teaching the high viscosity HPMCs are useful for sustaining action. Thus one having the knowledge available in the pharmaceutical arts would not be motivated to use a low viscosity rather than a high viscosity HPMC for the formulations in view of Akiyama's general disclosure. Given the broad scope of Akiyama's recited genera, even if the polyglycerol fatty acid is substituted by a glyceral behenate, combining Akiyama's genera would present countless formulation permutations and one of skill in the art could not reasonably predict which would be a suitable controlled release formulation for clarithromycin. As such Akiyama combined with Farah does not teach or suggest Applicants' particularly claimed control-release formulation.

In view of the forgoing remarks and amendments to the claims, Applicants request that the Office reconsider and withdraw the rejection of the claims under 35 U.S.C. §103 over Akiyama in view of Farah.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #104101.B700017).

Respectfully submitted,

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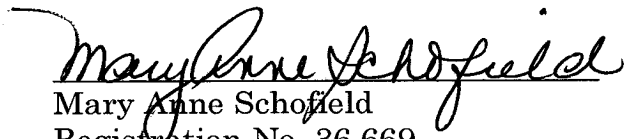

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